SCIENTIFIC ABSTRACT

High-Dose Chemotherapy and Autologous Bone Marrow plus Peripheral Blood Stem Cell Transplantation for Patients with Lymphoma or Metastatic Breast Cancer: Use of Marker Genes to Investigate the Biology of Hematopoietic Reconstitution In Adults.

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Autologous bone marrow transplantation (ABMT) is increasingly being used to rescue the bone marrow function after high-dose chemotherapy in patients with lymphoma and breast cancer. Over the past decade, transplantation of peripheral blood progenitor cells (PBPC) has emerged as an important method for hematopoietic rescue after high-dose chemotherapy, instead of ABMT or to supplement ABMT. This is conceivable because hematopoietic progenitor and possible stem cells circulate in the blood and can be collected by leukapheresis.

Little is known of the biology of autologous bone marrow (BM) graft recovery. Sustained hematopoiesis requires a population of multipotential stem cells capable of self-renewal and differentiation to various cell lineages. More mature progenitor cells, even though capable of proliferation and multipotential differentiation, have a more limited self renewal capacity. It is unknown, for example, if cryopreserved marrow contains viable stem cells to allow long-term engraftment or whether the autograft only provides temporary replenishment of committed progenitor cells. The biology of hematopoiesis from peripheral blood derived cells is even less clear. Since the BM is normally the site of hematopoiesis throughout life, there have been some concerns that PBPC may not contain the appropriate repopulating stem cells necessary for long term engraftment. It is also unknown if stem cells circulating in the blood differ from their corresponding BM counterparts.

The mechanism of relapse after high-dose chemotherapy and ABMT or PBPC transplantation in patients with breast cancer and lymphoma is also unknown. The intensive treatment may be insufficient to overcome tumor cell resistance but it is also possible that reinfused occult tumor cells may survive cryopreservation and contribute to relapse. Whether BM or peripheral blood derived cells differ in this respect is unknown. This is important, since if elimination of residual cancer cells is essential to the success of high-dose therapy, then methods of tumor "purging" are fully justified. If PBPC contribute less to relapse than BM derived cells, then PBPC transplantation would be a preferable approach. On the other hand, if the cause of relapse is not related to transfer of occult cancer cells, improving the pretransplant regiment may be more important.

Because autologous BM and blood progenitor cells are genetically identical to all other cells in the recipient, it is impossible to determine the precise origin of long-term post-transplantation hematopoiesis with present (non-gene transfer) technology. The current trial will mark cells in transplanted BM and PBPC progenitors with two distinguishable genes contained in near-identical retroviral vectors (LNL6 and GINa) carrying the Neo^R gene. Detection of marked hematopoietic cells after transplantation will allow us to trace their origin, to the transplanted BM or PBPC. If genetic tumor cells are detected after transplantation, we could also trace their origin to the reinfused PBPC or bone marrow cells. In this clinical trial, 10 patients with lymphoma or breast cancer will be studied.

The details of the vectors GINa and LNL6 have been reviewed and approved by the RAC in

several previous protocols and no changes have been made in them. The vectors will be supplied by Genetic Therapy, Inc., Gaithersburg, MD.